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A Study of the Effect of Antihistamine on Clinical Allergy Skin Testing

James Glazebrook Billingsley
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A STUDY OF THE EFFECT OF ANTIHISTAMINE ON CLINICAL

ALLERGY SKIN TESTING

by

James Glazebrook Billingsley
Captain, Medical Corps, U. S. Army

B.A., University of Oklahoma, 1952

M.D., University of Oklahoma, 1955

Date

August 3, 1960

A Thesis submitted to the Faculty of the Graduate

School of the University of Colorado in partial

fulfillment of the requirements for the Degree

Master of Science

Department of Medicine

1960

Billingsley, James Glazebrook (M.S., Medicine)

A Study of the Effect of Antihistamine on Clinical Allergy

This Thesis for the M.S. degree by

Skin Testing

James Glazebrook Billingsley

Thesis directed by Professor Joseph H. Holmes, M.D.

has been approved for the

In the modern practice of Allergy, it is occasionally

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benzamine or Benadryl.

Kim T. Joyce
Joseph H. Holmes

A double blind study was designed to evaluate the effect

of oral doses of antihistamine within the currently accepted

therapeutic range. The patients studied included both reactors

and nonreactors. The antihistamine utilized was Pyribenzamine,

and a placebo was obtained for the fifty milligram tablet. Over

seventy-five patients were challenged with two sets of ten intra-

dermal injections, and results were tabulated before the double

blind code was broken.

This study indicated the need for further study in the range

of nonreactors and very strong reactors. Analysis demonstrated no

significant effect of antihistamine on intradermal wheals.

Date August 3, 1960

Billingsley, James Glazebrook (M.S., Medicine)

A Study of the Effect of Antihistamine on Clinical Allergy

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I recommend its publication.

In the modern practice of Allergy, it is occasionally necessary or convenient to perform routine diagnostic skin testing while the patient is taking antihistamines. Current texts contain general statements that antihistamines depress skin reactions, but no quantitative data are given. Present concepts are based on work done with antigen challenge in sites locally injected with Pyribenzamine or Benadryl.

A double blind study was designed to evaluate the effect of oral doses of antihistamine within the currently accepted therapeutic range. The patients studied included both reactors and nonreactors. The antihistamine utilized was Pyribenzamine, and a placebo was obtained for the fifty milligram tablet. Over seventy-five patients were challenged with two sets of ten intradermal injections, and results were tabulated before the double blind code was broken.

This study indicated the need for further study in the range of nonreactors and very strong reactors. Analysis demonstrated no significant effect of antihistamine on intradermal wheals.

Antihistamines may be used to suppress systemic effects of antigen challenge, while skin reactions serve as a guide to hyposensitization therapy.

This abstract of about 177 words is approved as to form and content. I recommend its publication.

Signed

Joseph H. Holmes

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A STUDY OF THE EFFECTS OF HISTAMINE ON CLINICAL ALLERGY SKIN TESTING

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the reaction A STUDY OF THE EFFECT OF ANTIHISTAMINE ON CLINICAL ALLERGY SKIN TESTING

to look for the compound in actual states of allergic reaction. In
by James Glazebrook Billingsley, Captain, MC, U.S. Army
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whealing reaction of dermatographism, urticaria factitia, and food

allergy (12).

CHAPTER I

THE HISTORY OF MODERN ALLERGY

From that knowledge, several centers concentrated a search

for a Man's reaction to his environment involves numerous complex systems all geared for survival. On occasion, one of the reaction systems fails to offer protection and actually becomes a deadly threat. Anaphylaxis involves such a reaction (14). The specialty of Allergy is based on the need to reduce untoward reactions of man to his world and, sometimes, to himself.

Not all allergic reactions are severe nor seem to represent synthesis of KP 2339, Antergan. The initial report of the successful hypersensitivity at a dangerous level. Physicians have studied this clinical trial with this drug was made by Halpern and his group in type of phenomenon and its symptoms for less than sixty years (20).

1942. With this, the era of histamine antagonists or so-called The first ten years of this century produced three different study antihistamines was opened in the field of Allergy (12). approaches in Germany, France, and the United States. The basis for

present-day allergy practice evolved in these schools (3, 11). By 1909, the general framework for the theory of anaphylaxis was proposed. At that time, Dale and Lardlaw implicated histamine as important in hypersensitivity reactions.

trial revealed varied effectiveness in reducing the clinical symptoms Early histamine research. Although it was soon recognized noted in anaphylaxis in humans. It is stressed that the very best of that histamine was not the only factor involved in allergic responses, the antihistamines known today produces only limited protection and the study of the pharmacology of this compound shed great light on the concept of anaphylaxis (11). Since histamine produced many of

the reactions of anaphylaxis (26, 1), Lewis and Grant were stimulated to look for the compound in actual states of allergic reaction. In 1926, they reported the similarity of histamine wheals and the whealing reaction of dermographism, urticaria factitia, and food allergy (12).

Although the newer compounds have reduced side effects and increased primary From that knowledge, several centers concentrated a search for a satisfactory method of counteracting the histamine effect in allergic reactions in man. When histaminase and histamine desensitization failed, certain sympathomimetic compounds were investigated. Although many had limited promise, side effects far outweighed the benefits. Bovet and Staub reported in 1937 that phenolic ethers blocked certain of the actions of histamine. Initial use in animals proved the first compounds to be too toxic. Further study led to the synthesis of RP 2339, Antergan. The initial report of the successful clinical trial with this drug was made by Halpern and his group in 1942. With this, the era of histamine antagonists or so-called antihistamines was opened in the field of Allergy (12).

Other compounds were soon developed which appeared to counteract many of the manifestations of anaphylaxis in man. Research demonstrated the ability to reduce whealing, capillary permeability, and bronchospasm caused by the injection of histamine (4). Clinical trial revealed varied effectiveness in reducing the clinical symptoms noted in anaphylaxis in humans. It is stressed that the very best of the antihistamines known today produces only limited protection and

symptomatic coverage in the treatment of allergic reactions. None offers a true basis for attacking the hypersensitivity problem at its source.

One of the earliest criteria for the use of antihistamine was based on its ability to counteract skin whealing when introduced locally in the skin. Such techniques were even used as an early assay primary antihistamine activity, the only true present-day basis for to determine the relative strengths or physiological potency of new treatment of allergy at a cause and effect level remains in the antihistamines as they were introduced on the market (25). realm of hyposensitization to antigens responsible for symptoms.

Since the development of skin testing techniques and hyposensitization therapy, no single approach has offered more specific or effective therapy in the hypersensitive state. Thus, skin testing remains important in the management of allergic disorders (20).

The history taken from the allergic patient will often outline of testing and then allergens were injected (22). Other investigators the specific areas of an individual's hypersensitivity, and the use of used iontophoresis to introduce antihistamine through the epidermis skin testing procedures now serves as a guide to diagnosis and therapy. prior to injection of test solutions (2, 24). Oral antihistamine in In 1912, Schloss clearly demonstrated the correlation between sensitivity to egg and the positive skin test to the same protein. Further little was known of the absorption, distribution, and true action of interest was generated when Clowes produced skin whealing in reaction antihistamines, it was generally concluded that the drugs reduced to intradermal injection of extract of ragweed pollen. The total whealing on human skin, if the concentration was high enough in the scope of testing procedures and techniques expanded quickly as Cooke area where the allergens were introduced. Textbooks on Allergy still and his group investigated the widening area of skin reactions and contain the caution that skin tests in the allergic patient are published their reports during 1915 and 1916 (8). unreliable if the person has been on enough antihistamine to control

symptoms (29). Doses used to depress the skin test reaction in early studies appeared to be quite high for therapeutic purposes. The

The use of skin testing to evaluate antihistaminic activity.

Skin testing procedures were well established in clinical and investigative use when the first antihistamines were made clinically available. One of the earliest criteria for the use of antihistamine was based on its ability to counteract skin whealing when introduced locally in the skin. Such techniques were even used as an early assay to determine the relative strengths or physiological potency of new antihistamines as they were introduced on the market (25).

Arbesman injected Pyribenzamine in serial dilutions intradermally into human subjects and followed, after an interval of forty-five minutes, with allergen challenge. Both in direct testing and in passive transfer, a generalized reduction in whealing was noted (4). Antihistamine ointment was rubbed into the local areas of testing and then allergens were injected (22). Other investigators used iontophoresis to introduce antihistamine through the epidermis prior to injection of test solutions (2, 24). Oral antihistamine in large doses appeared to have a similar depressive effect. Although little was known of the absorption, distribution, and true action of antihistamines, it was generally concluded that the drugs reduced whealing on human skin, if the concentration was high enough in the area where the allergens were introduced. Textbooks on Allergy still contain the caution that skin tests in the allergic patient are unreliable if the person has been on enough antihistamine to control symptoms (29). Doses used to depress the skin test reaction in early studies appeared to be quite high for therapeutic purposes. The

question arose concerning the possible reliability of skin tests done while the patient was using antihistamines for symptomatic control: was it really necessary to discard such tests as invalid?

Selection of patients. Patients were selected at random

A study devised to relate therapy with antihistamines to clinical interpretation of skin tests. With this question in mind, a double blind study was set up at Fitzsimons General Hospital in 1957 to attempt to clarify this single point.

The antihistamine chosen was Pyribenzamine. Because of the interest in testing the depressive effect of therapeutic doses of this drug, a total of 200 mg. was given in four divided doses daily. This compound was one of those first investigated and is referred to frequently in the reports of skin testing made in the 1947-to-1952 period (4, 14). Pyribenzamine is still considered one of the most active of the clinically useful drugs and, thus, would correlate the early work with the clinical experience of today. Placebos* were obtained to control the double blind method as carefully as possible.

An additional group was made up of hospitalized patients with no history of allergy in themselves or in any of their close blood relatives. The separate analysis of this group produced some data which were as thought provoking as the entire study in itself.

Method of giving drugs. Patients were given eight pills coded and bottled by the pharmacy staff with the label, "Pyribenzamine, one every six hours." Both placebo and antihistamine were packaged identically, and no attempt was made by the investigator to discover which was given. Additional instructions were given

*The assistance of Ciba in making available placebos for 50 m Pyribenzamine is gratefully acknowledged.

CHAPTER II

TECHNIQUE

Selection of patients. Patients were selected at random

over a two and one-half year period at a rate to permit a single

examiner to perform the entire testing procedure. There was a total of seventy-five patients tested during that length of time, each receiving at least two sets of skin tests. The patients tested were obtained, in most part, from the Allergy Clinic and were divided into three categories. The first group had received no previous skin tests other than screening by the staff of the

clinic and was receiving no medication. The second group was on active hyposensitization therapy for symptoms of hay fever, urticaria, or asthma. The third group was being treated with measures other than injection therapy for the above conditions.

An additional group was made up of hospitalized patients with no history of allergy in themselves or in any of their close blood relatives. The separate analysis of this group produced some Occasional duplicate readings were made by members of the Allergy Department staff in an added attempt to gain uniformity throughout

Method of giving drugs. Patients were given eight pills coded and bottled by the pharmacy staff with the label, "Pyribenzamine, one every six hours." Both placebo and antihistamine were packaged identically, and no attempt was made by the investigator to discover which was given. Additional instructions were given

each subject to insure that the final dose would be taken one hour prior to the time when skin tests were to be given. The only control of medication was an effort to insure that no patient be given the same bottle number twice. In the study, the results were tabulated according to the drug which the patient had received.

Skin testing procedure. After the eighth dose (400 mg. of Pyrribenzamine in forty-eight hours), the patient was tested with ten of the basic groups. Thus each patient was challenged with representative antigens selected from the following groups: pollens, inhalants, pollens, inhalants, solids, and occasionally foods. Over 80 different molds, and foods. The patients with records of previous testings specific antigens were utilized, chosen when possible by earlier test by the allergy staff received antigens which had produced significant reactions. Over fifty tests were repeated to weed out, ash, cat hair, house dust, mold mix. Some antigens, such as mountain cedar, were used in only

to ten After the technique was established with the aid of the allergy staff, all of the testing was done by the author. A uniform wheal size of 3 mm. was maintained. The outer aspect of the arm was used in all cases with both sets of intradermal wheals placed on the same area. Prior to testing, the area was prepared with alcohol sponging and thorough drying. The tests were read after twenty minutes and recorded as zero to four plus, as described by Sheldon (2). Occasional duplicate readings were made by members of the Allergy Department staff in an added attempt to gain uniformity throughout the two and one-half year period during which the testing was accomplished. Each patient had a previously recorded negative test to rule out sensitivity to the diluent.

Each patient in the study received two separate sets of skin tests following two random courses of medication. In this manner, many of the patients acted as their own controls. When the code was broken at the completion of the study, the results were tabulated according to the drug which the patient had received.

In each patient representative antigens were given from several of the basic groups. Thus each patient was challenged with representative pollens, inhalants, molds, and occasionally foods. Over 80 different specific antigens were utilized, chosen when possible by earlier testing. Over fifty tests were repeated to ragweed, ash, cat hair, house dust, and mold mix. Some antigens, such as mountain cedar, were used in only eight to ten patients.

The reactions are divided into two groups. The first group is comprised of those who were given both the placebo and the antihistamine in random order and represent patients acting as their own controls. This group received one set of tests following antihistamine and another set following placebo. They should demonstrate the antihistamine effect, if any was present. The second group is comprised of those who received either the placebo or the antihistamine prior to both series of intradermal tests. This group represents the patients who, for the purposes of evaluation, received no drug at all and serve as controls. They reflect reproducibility of the procedure used.

Graphic presentation CHAPTER III results. The graphs pre-

sented list the initial or placebo reactions at zero to four plus.

RESULTS

The number on each graph represents the total number of patient

tests. Analysis of coarse data. Although interpretative data, as obtained by skin testing, does not lend itself to direct statistical evaluation, several methods were used to judge the results obtained in this study. Trend analysis, which is difficult to graphically present, did not show any significant alteration of the skin test, whether the patient was on antihistamine or placebo. Graphic analysis, as shown in Figures 1 through 6a, appeared to be the most satisfactory method of presenting the data.

The reactions are divided into two groups. The first group is comprised of those who were given both the placebo and the antihistamine in random order and represent patients acting as their own controls. This group received one set of tests following antihistamine and another set following placebo. They should demonstrate the antihistamine effect, if any was present. The second group is comprised of those who received either the placebo or the antihistamine prior to both series of intradermal tests. This group represents the patients who, for the purposes of evaluation, received no drug at all and serve as controls. They reflect reproducibility of the procedure used.

The three columns of figures labeled "antihistamine" demonstrate comparative data for tests done after antihistamines, contrasted with those done in the same subjects after placebo. Of 661 pairs of tests, the center checkered column indicates that

Graphic presentation of testing results. The graphs presented list the initial or placebo reactions at zero to four plus. The number on each graph represents the total number of patient tests which reacted at each level, zero to four plus. The columns show how many of the second reactions were unchanged, increased, or decreased. Each graph represents the comparison between the first and second testing for each individual antigen. The graphs are arranged in pairs to facilitate comparison of the scatter seen in the control and antihistamine tests.

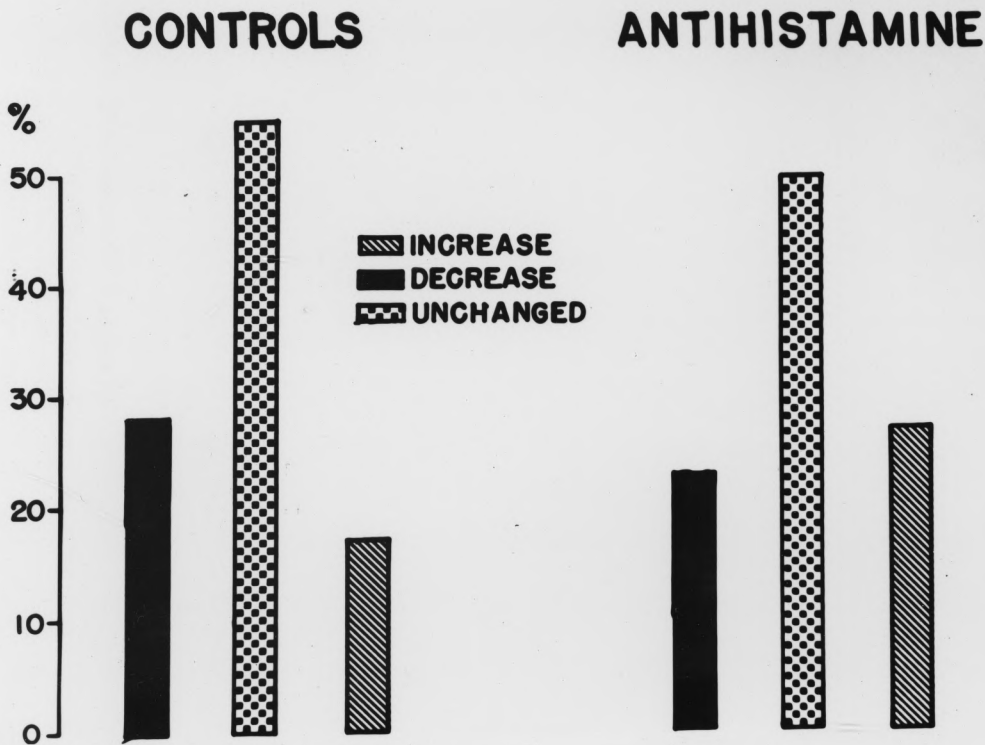
In Figure 1, the three columns under the heading "Controls" present the data on 199 tests which were repeated following duplicate drugs. These data represent results obtained in control subjects. The checkered center column reflects the 55% of tests to the different antigens which reacted at the same level when retested. The first, or solid black column, represents the 28% of tests which decreased on retesting. The striped column shows that 17% of the 199 tests increased in reactivity when retested. This graph reflects the reproducibility of the skin testing technique without any drug effect, since control patients received the same drug prior to both test sets.

Figure 1. Analysis of the two groups of patients showing per cent of tests which remained the same, increased, or decreased upon retesting.

The three columns of figures labeled "Antihistamine" demonstrate comparative data for tests done after antihistamines, contrasted with those done in the same subjects after placebo. Of 661 pairs of tests, the center checkered column indicates that

50% reacted at the same level following placebo and following anti-histamine. Twenty-three per cent of the test reactions decreased, as represented by the solid black bar, and 27% reacted more strongly on antihistamine than on placebo.

CONTROLS vs ANTIHISTAMINE ANALYZED AS A GROUP



six to three plus, a total of 41% of the repeated tests showing a

Figure 1. Analysis of the two groups of patients showing per cent of tests which remained the same, increased, or decreased upon retesting.

In Figure 2a, the zero reactors of the control or no-drug group are shown. Of the forty-two zero tests on initial studies, thirty (71%) were also zero on second testing. Ten tests increased to one plus and two to three plus, for a total increase of 29%. No tests reacted two plus or four plus.

50% reacted at the same level following placebo and following antihistamine. Twenty-three per cent of the test reactions decreased, as represented by the solid black bar, and 27% reacted more strongly on antihistamine than on placebo.

The distribution in these two groups portrays the information obtained by trend analysis--that the scatter of change in patients is as great when routinely retested as it is when they are tested with placebo and then with antihistamine.

Figures 2 through 6a reflect a breakdown of Figure 1 into graphs, representing each of the possible levels of reaction, from zero to four plus. Each pair of illustrations shows the changes shown by the antihistamine group in direct comparison with the same level of reactivity in tests done on the control subjects.

Figure 2 outlines the 173 tests on antihistamine patients which reacted at zero on initial challenge following placebo. Upon retesting after antihistamine, 102 tests (59%) remained at the zero level. Fifty-one tests rose to one plus, fourteen to two plus, and six to three plus, a total of 41% of the repeated tests showing a tendency to increase under antihistamine effect.

histamine could remain zero or increase. Note number of tests and per cent are presented.

In Figure 2a, the zero reactors of the control or no-drug group are shown. Of the forty-two zero tests on initial studies, thirty (71%) were also zero on second testing. Ten tests increased to one plus and two to three plus, for a total increase of 29%. No tests reacted two plus or four plus.

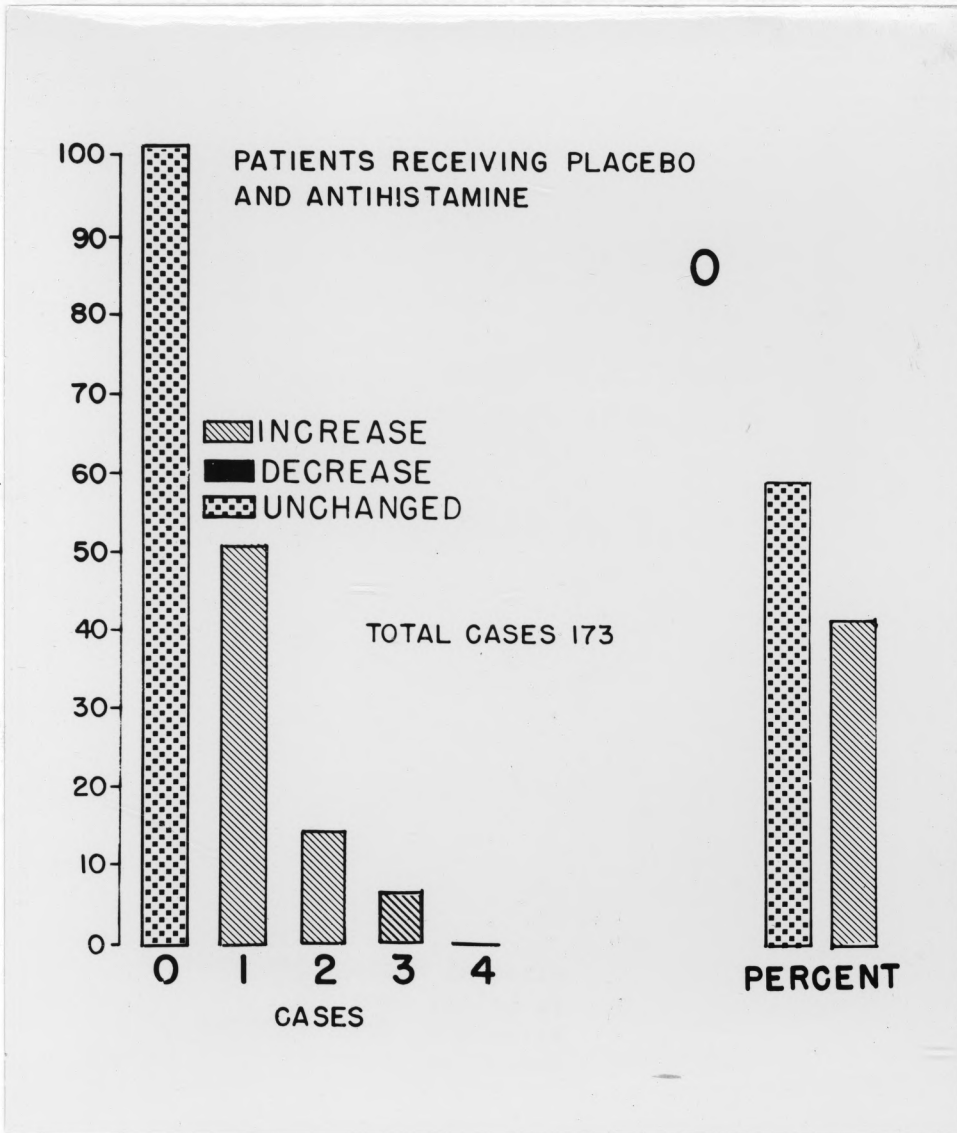


Figure 2. The zero reactions when retested following anti-histamine could remain zero or increase. Note number of tests and per cent are presented.

Figure 3 details the tests which were initially one plus

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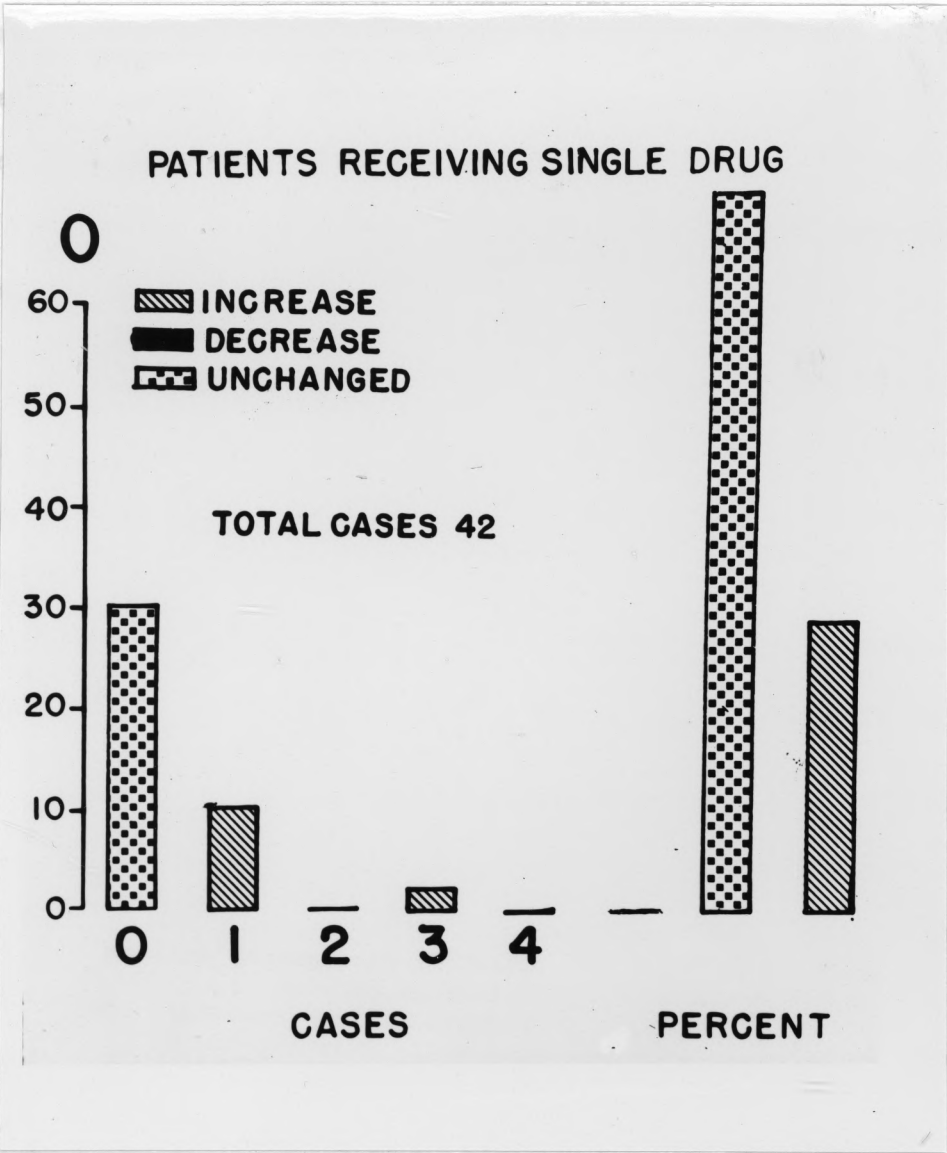


Figure 2a. Zero reactors in the control or no drug group.

group. Upon retesting, fifteen (37%) were unchanged. Seventeen fell

to one plus and two to zero, a decrease of 46%. In the two plus con-

trol group, four tests rose to three plus and three to four plus on

retesting, a total increase of 17%.

Figure 3 details the tests which were initially one plus following placebo. Of the 163 in this group, seventy (43%) remained at the one plus reaction on retesting. Thirty-five tests fell to zero on retesting, a decrease of 21%. On antihistamine, forty-one tests rose to two plus, twelve to three plus, and five to four plus, an increase of 36%.

Figure 3a includes fifty-five tests with an original reaction of one plus on no drug. Twenty-eight of the repeated tests remained at the one plus level, for a total of 51% unchanged. Sixteen of the repeated tests fell to zero, showing a total decrease of 29%. The 20% which rose in reactivity consisted of nine tests which rose to two plus and two which rose to three plus.

Figure 4 illustrates 108 tests which reacted at the two plus level following placebo. Upon retesting following antihistamine, thirty-three (31%) remained two plus. Forty-four tests fell to one plus and nine fell to zero, a decrease of 49% of the tests when repeated under Pyribenzamine effect. Seventeen tests rose to three plus and five to four plus, an increase of 20%.

Figure 4a reflects the forty-one two plus tests in the control group. Upon retesting, fifteen (37%) were unchanged. Seventeen fell to one plus and two to zero, a decrease of 46%. In the two plus control group, four tests rose to three plus and three to four plus on retesting, a total increase of 17%.

PATIENTS RECEIVING PLACEBO AND ANTIHISTAMINE

| +

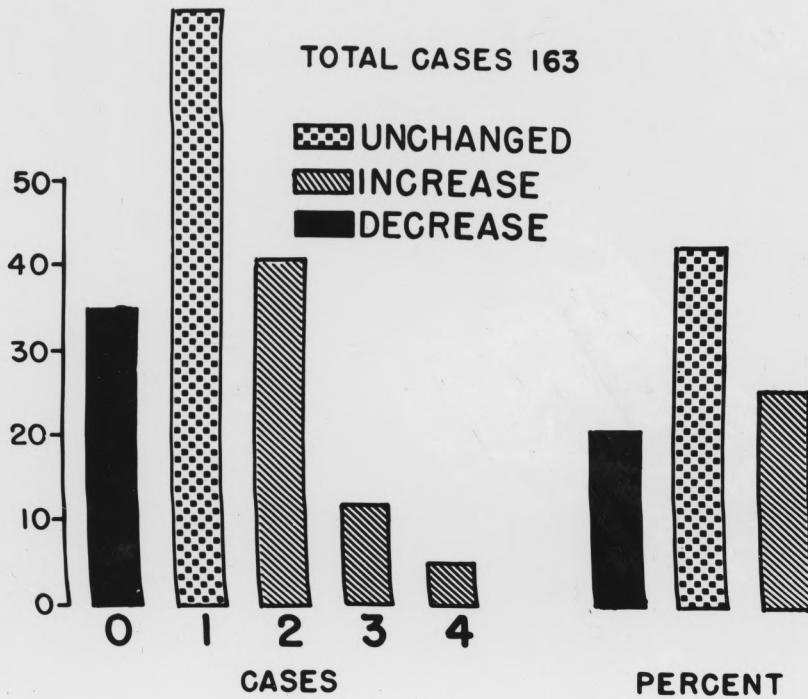


Figure 3. One plus reactions following placebo could remain the same, increase, or decrease when challenged after antihistamine.

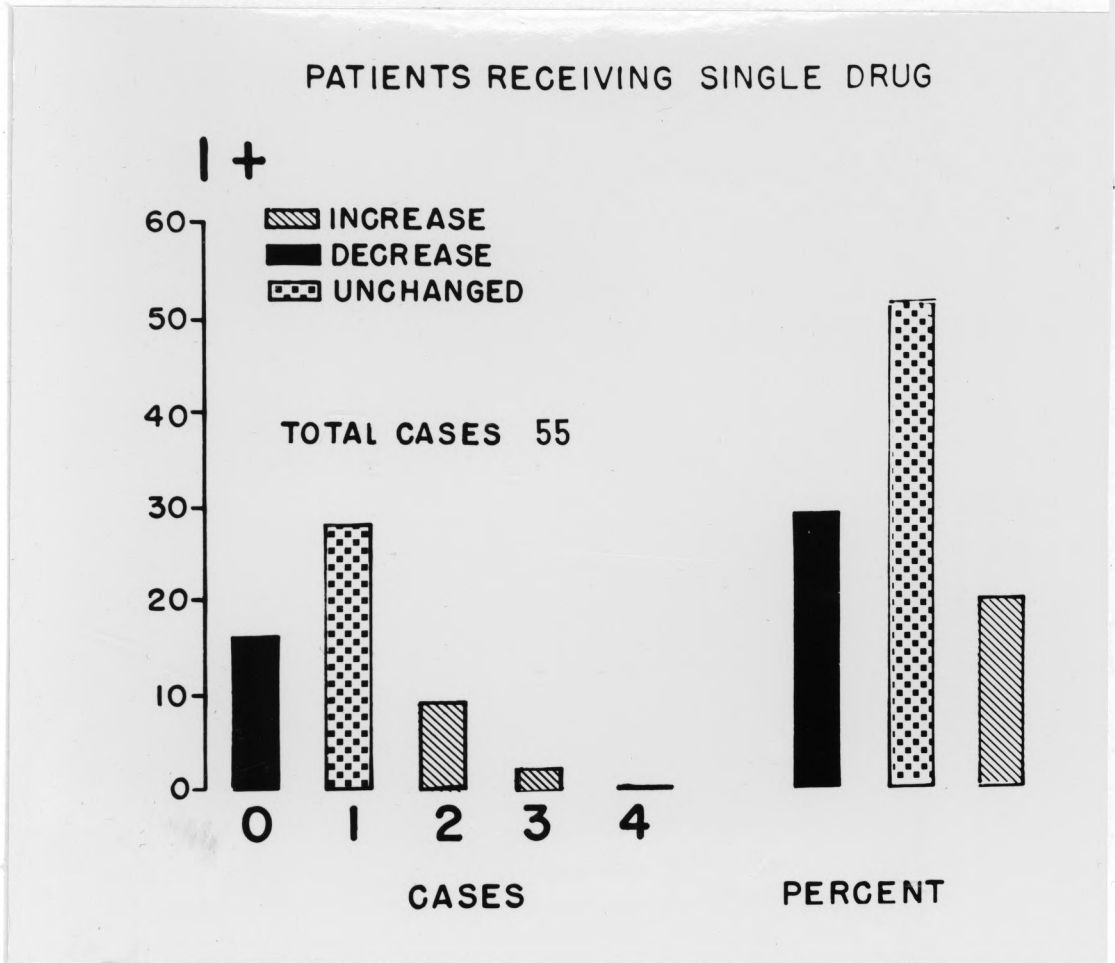


Figure 3a. One plus reactions in the no drug control group with second tests at the same, decreased, or increased levels of reactivity.

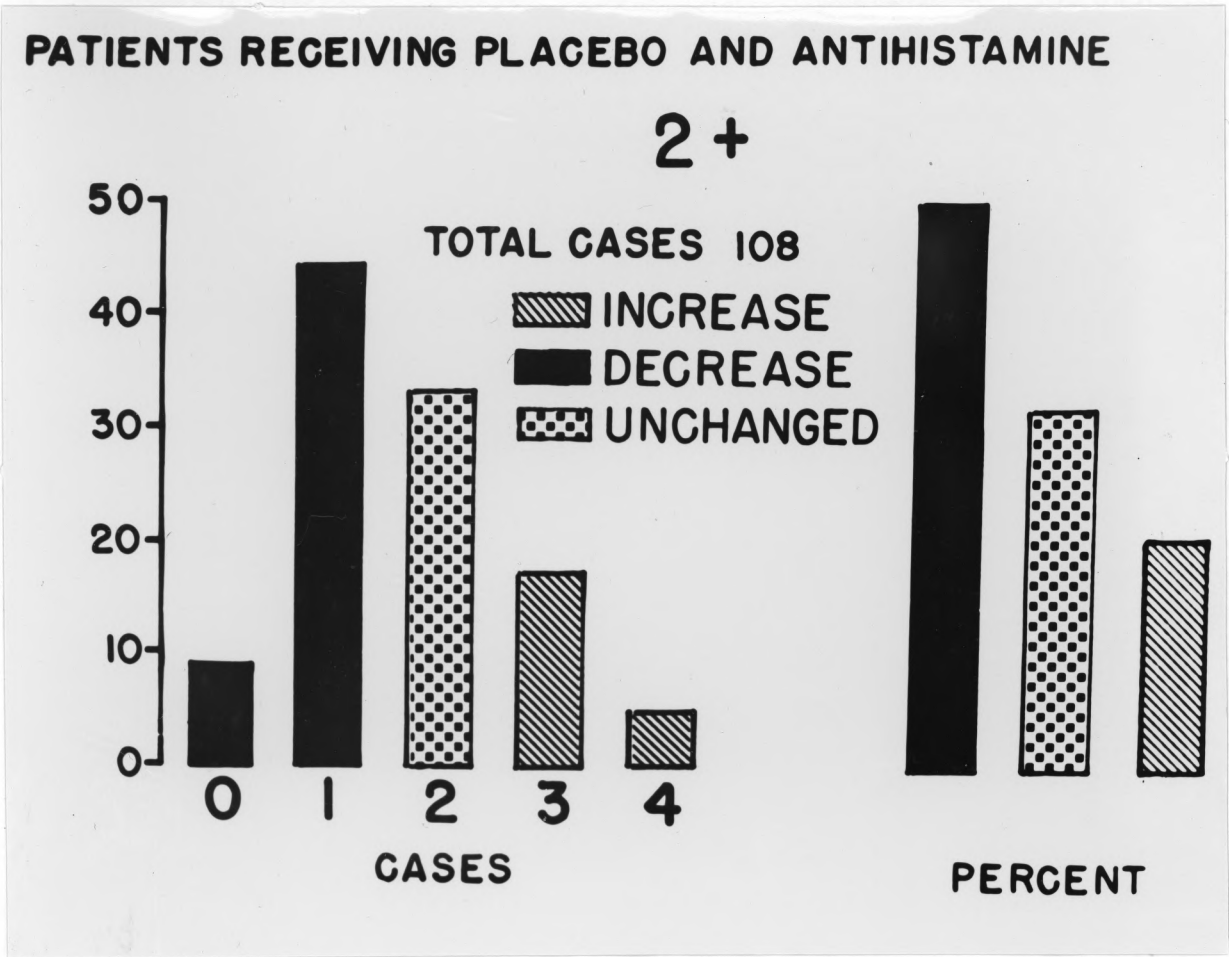


Figure 4. Two plus reactions on placebo with subsequent test reactions on antihistamine.

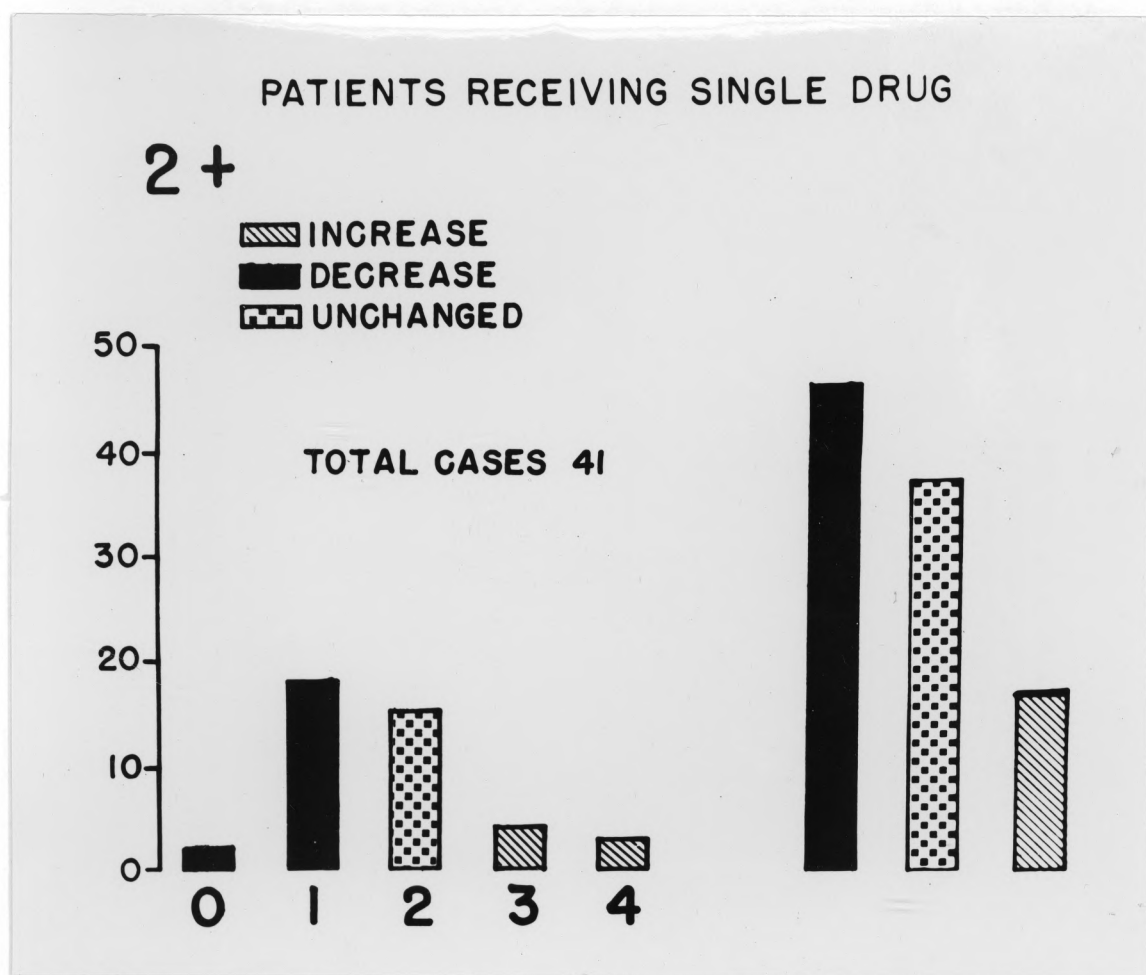


Figure 4a. Two plus reactions in the no drug control group with second tests at the same, decreased, or increased levels of reactivity.

Figure 5 represents 107 three plus tests following placebo. Thirty-six (34%) remained at three plus on retesting after anti-histamine. Thirty-four tests fell to two plus, twenty-two to one plus, and three to zero on retesting, for a 55% decrease on anti-histamine. A total of twelve tests (11%) rose to four plus on retesting.

Figure 5a shows twenty-seven control tests which were initially three plus reactive. In this group, fourteen (52%) were unchanged on retesting. Seven tests fell to two plus and three to one plus, a decrease of 37%. Three tests rose to four plus, an 11% increase.

Figure 6 represents 110 tests following placebo which reacted four plus. Upon retesting under antihistamine effect, sixty-three (57%) were unchanged. Twenty-four tests fell to three plus, twenty to two plus, and three to one plus, a decrease of 43%.

Figure 6a depicts thirty-four tests on control subjects which initially reacted four plus. Twenty-three (67%) were unchanged on retesting. Eight fell to three plus, two to two plus, and one to one plus, for a total decrease of 33%.

PATIENTS RECEIVING PLACEBO AND ANTIHISTAMINE

3 +

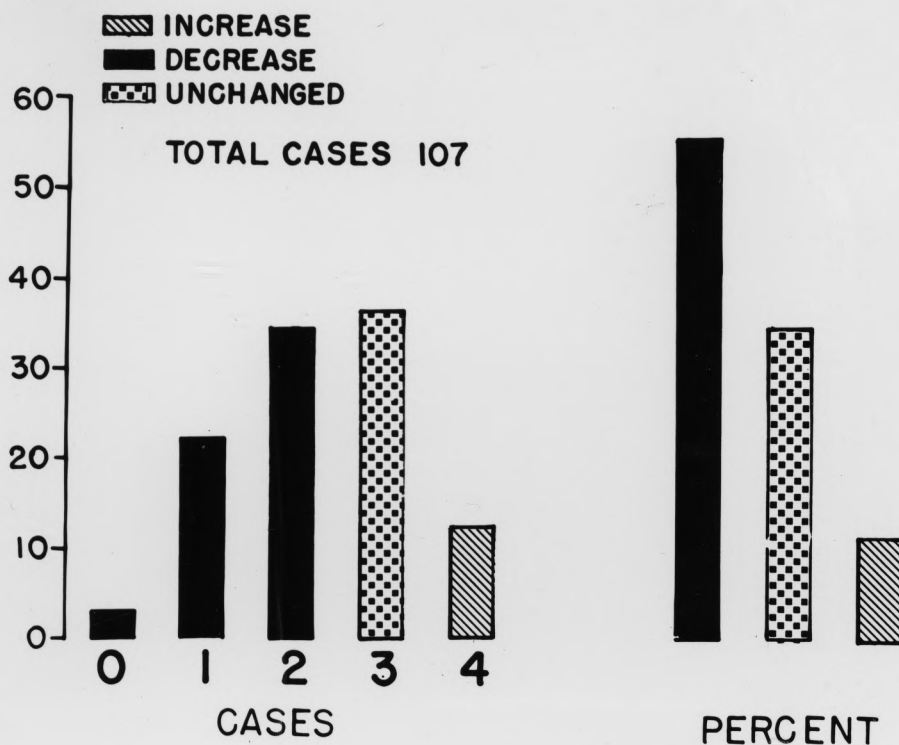


Figure 5. Three plus reactions on placebo with subsequent antihistamine test reactions.

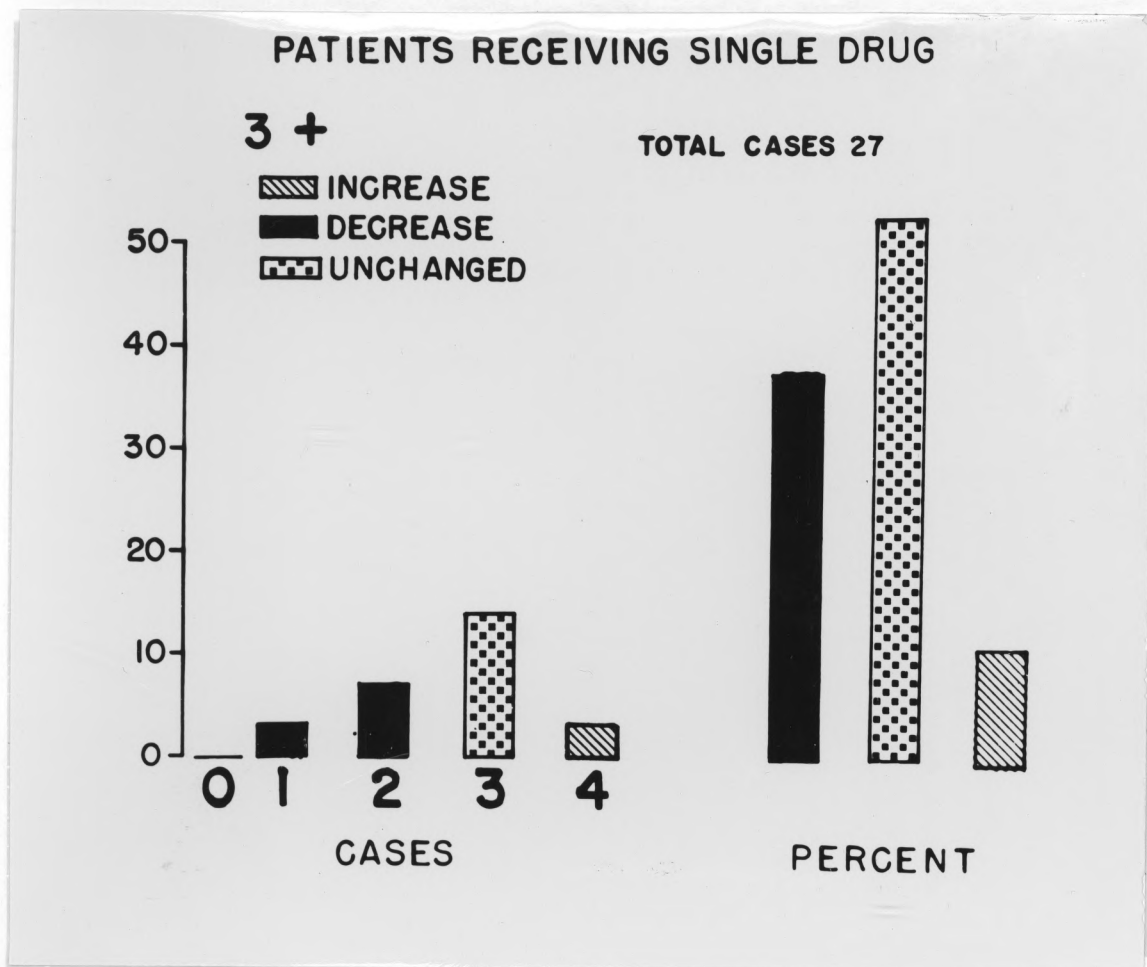


Figure 5a. Three plus reactions in the no drug control group with second tests at the same, decreased, or increased levels of reactivity.

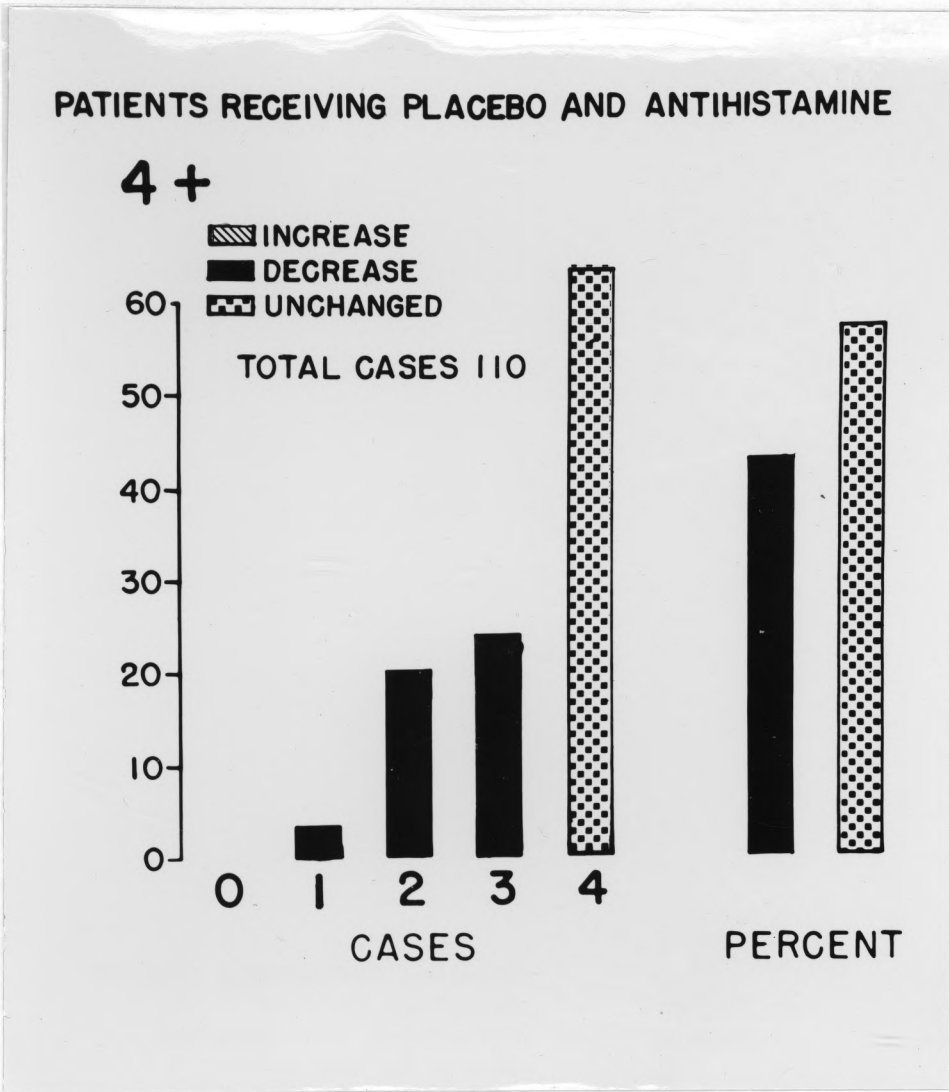


Figure 6. The four plus reactions when retested following antihistamine could remain at four plus or decrease.

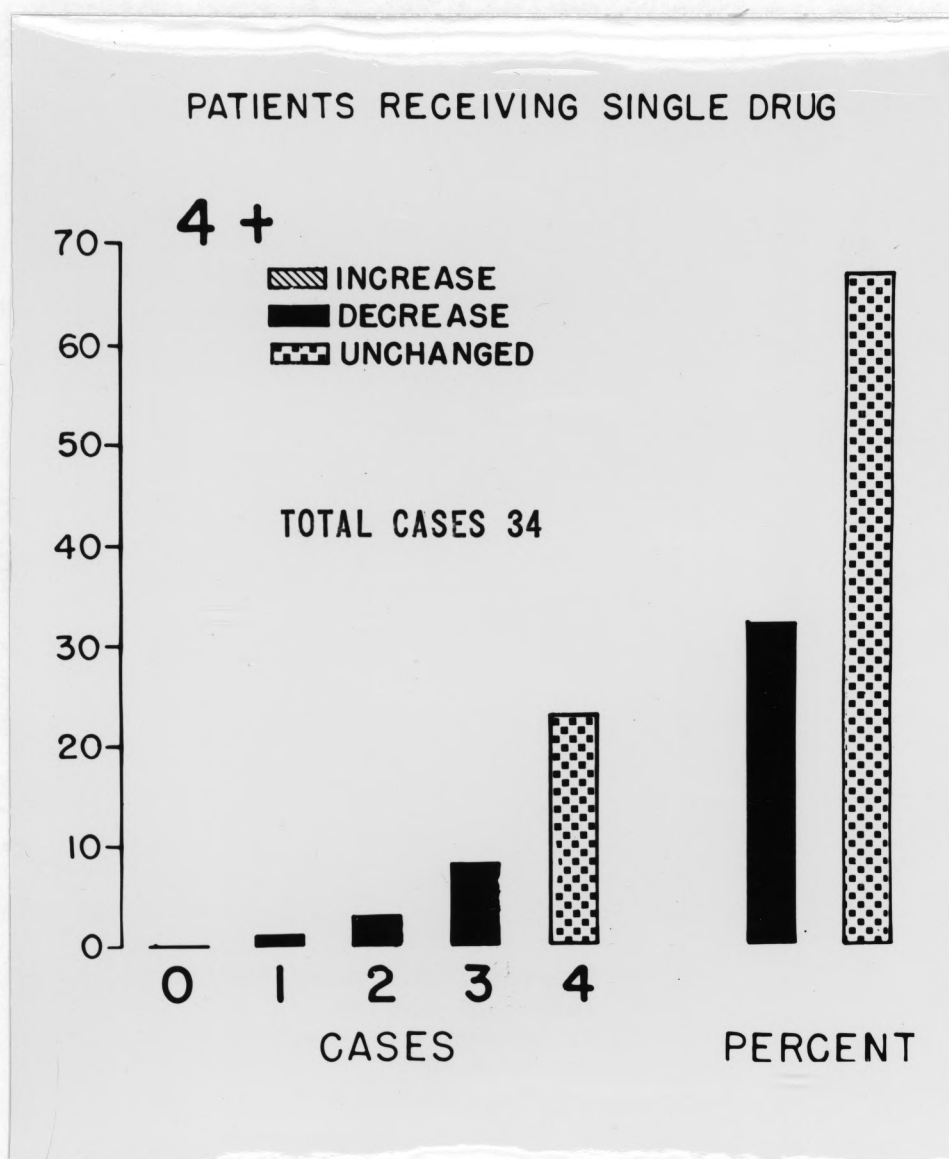


Figure 6a. Four plus reactions in the control group.

CHAPTER IV

DISCUSSION

General trend seen in data. The variation seen when the group tests were analyzed at zero, one plus, and two plus reactions (Figures 2-4a, pages 13, 14, and 16-19) is quite similar in both the control patients and those who received both drugs. At the higher levels of reaction, three and four plus (Figures 5-6a, pages 21-24) there seems to be a greater tendency for the antihistamine to show some depression when compared to tests following placebo.

It is emphasized that the downward trend did not remain uniform in any individual patient, and one who showed a single test change from four plus on placebo to two plus on antihistamine frequently had the opposite change on other tests. Thus, no patient showed a strong general trend for all or most of the four plus reactions to decrease on antihistamines but demonstrated the characteristic only occasionally. The exception is one case in whom the downward trend was uniform and in whom the antihistamine tests were all lower than the tests recorded following placebo.

All skin reactions do not offer good basis for study.

The zero reactions and the four plus reactions do not offer good test comparison, since the change in either of these groups can only be in one direction. These two categories have a tendency to balance each other but do not add to the individual analysis of the data

except by their weight in studying general trends. If further testing were to be done, it is felt that the two and three plus reactions might offer the best range for study since these can respond both upward and downward and offer the best basis for analysis of results. These reactions are the most sensitive to change. The slight downward trend in the three and four plus reactions suggests the need for further study in this

Additional studies on selected drug forms. After collection and analysis of the data on the above groups of patients, several smaller groups were tested to study the possibility that results obtained were totally the chance of the technique employed. Five patients were challenged with wheals measuring 5 mm., and this group showed results similar to the seventy-five in the original study.

Another six patients were given Pyribenzamine Lontabs to assess the possibility that blood levels had varied in the previous series. This group also reacted in the same manner and degree as the original group.

Positive skin tests found in persons who had no allergic history. It is of interest to note that the reactions of the group of nine patients who had no atopic or personal allergic history revealed that three had highly positive intradermal reactions. These were nonreactive to the diluent and had several strongly positive four plus tests. Careful questioning upon reviewing test results failed to disclose any signs or symptoms of allergy.

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CHAPTER V

CONCLUSIONS

The general data imply that oral antihistamines at therapeutic doses do not interfere with the intradermal skin testing as clinically performed by the allergist. The slight downward trend in the three and four plus reactions suggests the need for further study in this group.

A second fact brought out by the study is that the skin testing procedure is reproducible well within the useful limits of biological variation. A significant number of patients had identical tests on repeated challenge.

It is concluded that the effect of antihistamines on skin testing is negligible, and this group of drugs can be used to control symptoms while the allergist is attempting to select specific allergens for hyposensitization therapy.

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